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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK,
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Published:

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- before the expiration of the time limit for amending the
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PREVENTION OF FLAP NECROSIS IN PLASTIC SURGERY

(57) Abstract: NO, NO donor or prodrug that causes formation of nitrosothiol in tissue optionally in combination with lidocaine is topically applied to pedicle of a pedicle flap or other source of blood supply to prevent necrosis in pedicle flap or in any microvascular surgery. Composition containing drug is formulated with nitrosylated polythiolated cyclodextrin to improve drug delivery.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/36138

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 21/90; C07D 405/14

US CL : 568/949; 564/300, 301; 558/480, 488; 534/568

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 568/949; 564/300, 301; 558/480, 488; 534/568

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,403,759 B2 (STAMLER et al) 11 June 2002 (11.06.2002), entire documents, especially column 1, lines 13-39; column 2, line 11 thru column 3, line 56; claims.	4-5 and 7-8
Y	US 6,359,182 B1 (STAMLER et al) 19 March 2002 (19.03.2002), see entire documents.	4-5 and 7-8
Y	Database CAPLUS on STN Online, No. 1997:786946, KIM et al. 'Nitric Oxide Prevents the Bovine Cerebral Endothelial Cell Death Induced by Serum-Deprivation,' abstract, Korean Journal of Physiology & Pharmacology, 1997, 1(5), 515-521.	4-5, 7-8
Y	Database CAPLUS on STN Online, No. 1996:184698, FARINELLI et al. 'Nitric Oxide Delays the Death of Trophic Factor-Derived PC12 Cells and Sympathetic Neurons by a cGMP-Mediated Mechanism,' abstract, Journal of Neuroscience, 1996, 16(7), 2325-34.	4-5, 7-8

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

07 November 2003 (07.11.2003)

Date of mailing of the international search report

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Name and mailing address of the ISA/US

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/36138

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 1-3 and 6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US02/36138

Continuation of Box I Reason 2:

Claims 1-3 and 6 relate to an extremely large number of possible composition comprising "NO or NO donor or prodrug that causes formation of nitrosothiol in tissue", "alkyl nitrite of molecular weight up to 10,000", "alkyl nitrite is ethyl nitrite" or "a methal nitrosyl". Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely S-nitrosothiol or cyclodextrin NO

Continuation of B. FIELDS SEARCHED Item 3:

STN ONLINE

search terms: S-nitrosothiols, S-nitrosoglutathione, S-nitroso-N-acetylpenicillamine, S-nitroso-cysteine, S-nitroso-gamma-methyl-L-homocysteine, S-nitroso-L-homocysteine, S-nitroso-gamma-thio-L-leucine, S-nitroso-delta-thio-L-leucine, S-nitrosoalbumin, nitrosylated polythiolated cyclodextrin, cyclodextrin NO, CX-NO, S-nitrosylated beta-cyclodextrin